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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/731,660 | 12/08/2000 | Haruhiko Kouhara | 038602/1023 | 1711 |

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| EXAMINER |
|---|
| HUTSON, RICHARD G |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 04/23/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application N . | Applicant(s) | |
|---|---|---|---|
| | 09/731,660 | KOUHARA ET AL. | |
| | Examiner | Art Unit | |
| | Richard G Hutson | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) 1-6,11-13 and 19 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6,11-13 and 19 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Applicants preliminary amendment of claims 13 and 19 and cancellation of claims 7-10 and 14-18, Paper No. 1.5, 12/8/2000, is acknowledged. Applicants amendment of the specification, Paper No. 3, 6/4/2001, is acknowledged. Claims 1-6, 11-13, and 19 are at issue and are present for examination.

### *Information Disclosure Statement*

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

### *Drawings*

The drawings are objected to for the reasons stated on the Notice of Draftpersons Patent Drawing Review (PTO-948).

Correction is required.

### *Specification*

The disclosure is objected to because of the following informalities:

Application serial number 08/980,523 has issued as a U.S. Patent. It is suggested that applicants update this information in the first line of the specification.

On page 24, line 8 through page 25, line 5 of the specification, applicants recite as another aspect of the invention a recitation of claim 11. This is objected to for each of the reasons that claim 11 is rejected based on indefiniteness under 35 USC 112, below.

Appropriate correction is required.

### *Claim Objections*

Claims 1-6, 11-13, and 19 are objected to because of the following informalities:

Claims 1-6, 11-13, and 19 each recite "FRS2 polypeptide" or depend from a claim which recites "FRS2 polypeptide". It is suggested that the first time in the claims the term "FRS2 polypeptide" is used it be written out in full, followed by the abbreviation in parenthesis.

Appropriate correction is required.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-6, 11-13, and 19 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1-6, 11-13, and 19 are indefinite in that it is unclear in the recitation "FRS2 polypeptide and FRS2 protein." While applicants teach that FRS2 stands for Fibroblast Growth Factor Receptor Protein Kinase Substrate 2" and regulates growth factor stimulation of cellular differentiation and cellular proliferation by linking stimulated fibroblast growth factor receptor (FGFR) to the Ras/MAPK cascade via the Grb-2/Sos complex, it remains unclear applicants intent in the recitation "FRS2 polypeptide". Applicants teach that the term "FRS2 polypeptide" refers to a polypeptide having an amino acid sequence preferably of at least 400 contiguous amino acids, more preferably of at least 450 contiguous amino acids, or most preferably of at least 508 contiguous amino acids set froth in Figure 1A, or is substantially similar to such a sequence. Applicants further teach that a sequence that is substantially similar to such a sequence will preferably have at least 90% identity (more preferably at least 95% and most preferably 99-100%) identity to the amino acid sequence of Figure 1A. Applicants further teach that FRS2 polypeptides preferably have Grb-2 binding activity. The recitation is indefinite in that while applicants prefer the "FRS2 polypeptide " to have a number of structural or functional activities, it remains unclear which of these preferred characteristics are necessary limitations of the polypeptide encoded by the claimed nucleic acid.

Claim 11 is further indefinite in the following "...nucleic acid molecule comprising a nucleotide sequence that ..." The claim then recites a number of possible properties of the claimed nucleic acid of the format (a)..., (b)..., (c)... through (k). Part (b) recites "the complement of..." It is believed that applicants intent was "**is** the complement of..."

Part (d) recites "a FRS2 polypeptide..." It is believed that applicants intent was "**encodes** a FRS2 polypeptide..." Part (e) recites "the complement of..." It is believed that applicants intent was "**encodes** a the complement of..." Part (f) recites "a polypeptide having..." It is believed that applicants intent was "**is** a polypeptide having..." Part (g) recites "the complement of..." It is believed that applicants intent was "**is** the complement of..." Part (i) recites "the complement of..." It is believed that applicants intent was "**is** the complement of..." Part (k) recites "the complement of..." It is believed that applicants intent was "**is** the complement of..." Part (j) recites "encodes a polypeptide of (a), (d) or (f) containing..." It is suggested that applicants amend this recitation to "encodes a polypeptide **as set forth in** (a), (d) or (f) containing...", since parts (a), (d) and (f) describe nucleic acids which encode polypeptides.

Claim 11 (c) (12, 13, and 19 dependent on) is indefinite in the recitation of "hybridizes under highly stringent conditions" as the specification does not define what conditions constitute "highly stringent". While page 9 , lines 14-page 10, line 2 of the specification discusses various embodiments of the present invention, specifically with respect to hybridization, there is nothing to suggest what conditions are included within the scope of this term and in the art what is considered stringent varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of a gene encoding the polypeptide of Figure 1A, a sequence must be to be included within the scope of these claims.

Claim 19 is further indefinite in that it depends from cancelled claims 18, 17 and 7. For the purpose of advancing prosecution this claim is interpreted as if it claim 18, 17 and 7 were still pending thereby incorporating all of the limitations of the claims.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 11-13 and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-6, 11-13 and 19 are directed to all possible nucleic acids encoding any FRS2 polypeptide and recombinant cells or tissues comprising said nucleic acid (claims 1, 5 and 6 ), where the nucleic acid is isolated from a mammal (claim 2), where the nucleic acid molecule encodes at least three contiguous amino acids of the full length amino acid sequence shown in Figure 1A (claim 3) and nucleic acid probes for the detection of a nucleic acid molecule encoding a FRS2 polypeptide (claim 4). Claims 11-13 are directed to all possible nucleic acids which hybridize under highly stringent conditions to the nucleotide molecule which encodes a polypeptide as set forth in Figure 1A and encodes a FRS2 protein or any nucleic acid which encodes a polypeptide comprising one or more of the FRS2 domains 1-10, 11-152, or 153-508 and vectors and host cells comprising said nucleic acids (Claims 11-13). The specification, however,

only provides a single representative species which encodes the FRS2 polypeptide having the amino acid sequence of SEQ ID NO: 1, encompassed by the claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these nucleic acids by any identifying structural characteristics. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1-6, 11-13 and 19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a nucleic acid encoding a FRS2 polypeptide, wherein said FRS2 polypeptide has the amino acid sequence of SEQ ID NO: 1, does not reasonably provide enablement for any nucleic acid encoding a FRS2 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir.

1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 1-6, 11-13 and 19 are so broad as to encompass any nucleic acid encoding any FRS2 polypeptide and recombinant cells or tissues comprising said nucleic acid (claims 1, 5 and 6 ), where the nucleic acid is isolated from a mammal (claim 2), where the nucleic acid molecule encodes at least three contiguous amino acids of the full length amino acid sequence shown in Figure 1A (claim 3) and nucleic acid probes for the detection of a nucleic acid molecule encoding a FRS2 polypeptide (claim 4). Claims 11-13 are so broad as to encompass any nucleic acid which will hybridize under highly stringent conditions to the nucleotide molecule which encodes a polypeptide as set forth in Figure 1A and encodes a FRS2 protein or any nucleic acid which encodes a polypeptide comprising one or more of the FRS2 domains 1-10, 11-152, or 153-508 and vectors and host cells comprising said nucleic acids (Claims 11-13).

The scope of the claims are not commensurate with the enablement provided by the disclosure with regard to the extremely large number of nucleic acids broadly encompassed by the claims. The claims rejected under this section of U.S.C. 112, first paragraph, only place minor if any structural limitations and no functional limits (See above 112 second paragraph rejection) on the claimed nucleic acids. Since the amino

acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleic acids encoding the FRS2 protein having the amino acid sequence of SEQ ID NO: 1, and does not define those additional characteristics of the protein necessary for inclusion in the claimed genus other than the amino acid sequence of SEQ ID NO: 1.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all modifications and fragments of any nucleic acid encoding a FRS2 polypeptide, because the specification does not establish: (A) regions of the protein structure which may be modified without effecting its activity; (B) the general tolerance

of a FRS2 polypeptide to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a FRS2 polypeptide with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful. Because of this lack of guidance, the extended experimentation that would be required to determine which substitutions would be acceptable to retain an activity and the fact that the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), it would require undue experimentation for one skilled in the art to arrive at the majority of those nucleic acids of the claimed.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any nucleic acid encoding any FRS2 polypeptide. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Claim R jections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 4 and 11 are rejected under 35 U.S.C. 102(b) as being anticipated by Ottilie et al. (Oncogene Vol 7, No 8: 1625-1630, August 1992).

Ottilie et al. teach identification and cloning of four different src-related tyrosine kinase genes (See page 1626, Figures 1 and 2). The taught nucleic acid encode a FRS2 polypeptide in as much as applicants have not taught what a FRS2 polypeptide is (See above 112 second paragraph rejection) and these nucleic acids encode at least three contiguous amino acids of the full length amino acid sequence shown in Figure 1A. Further, Ottilie et al. teach a nucleic acid probe to for the detection of the nucleic acid molecule encoding a FRS2 polypeptide (See page 1626, middle of left column). Further it is pointed out that the nucleic acid taught by Ottilie et al. encodes a polypeptide having the full length amino acid sequence of the sequence set forth in Figure 1A except that it lacks the following segments of amino acid residues: 1-10, 11-152, or 153-508, (part (d) of claim 11). Thus Ottilie et al. anticipates claims 1, 3, 4 and 11.

***Claim Rej ctions - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4, 5, 6, 11, 12, 13 and 19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wang et al.

Wang et al. teach that the existence of a class of proteins that are SNT-like (SLPs), expressed in fibroblast, myoblast and lymphoid cell lines, are phosphorylated in response to several mitogenic ligands, predominantly membrane associated, and are weakly associated with activated FGF receptor-1 suggesting that these proteins may be direct targets of the receptor kinase. Further Wang et al. show that the SLPs are associated with Grb-2 adaptor protein and Ras proteins. As discussed above, it is unclear what applicants intent is when reciting a "FRS2 polypeptide" (See 112 second paragraph rejection), thus based on many of the shared characteristics of the taught SLP protein of Wang et al. and that of the FRS2 protein of the instant application, as discussed above, those nucleic acids that encode a SLP protein are thought to be encompassed by those nucleic acids that encode a FRS2 polypeptide.

One of ordinary skill in the art at the time of filing would have been motivated to isolate and clone a nucleic acid encoding the SLP proteins taught by Wang et al. in order to express these SLP proteins recombinantly so that there role in signal

transduction and their involvement with the known oncogene ras. The many advantages of recombinant production of useful proteins are well known within the art as are recombinant methods of obtaining the necessary genes. These advantages include the ability to produce much larger quantities of the protein, being able to produce the protein in more easily handled organisms, reducing the number of steps necessary for the purification of a protein and producing the protein in a purer form by using an organism that does not include naturally occurring contaminants of the protein. The reasonable expectation of success comes from the high level of knowledge in the art with respect to the identification and isolation of nucleic acids that encode known proteins and the results of Wang et al. who teach the identification of cell types which express the SLPs as well as the size of the SLP proteins and their binding partners.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
April 22, 2002

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